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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/939,581	08/28/2001	Heiko Hermeking	01107.00187	3865

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BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
MCGARRY, SEAN	
ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/939,581	Applicant(s) HERMEKING ET AL.	
	Examin r Sean R McGarry	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-24 and 49-83* is/are pending in the application.

4a) Of the above claim(s) *1,2,6-13,24 and 49-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 9 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of Group IV, claims 14-23, in Paper No. 11, filed 3/20/03 is acknowledged.

Claims 1, 2, 6-13, 24, and 49-83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claims 14-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 1 which corresponds to the cDNA/genomic DNA encoding the human species of 14-3-3σ. Antisense constructs and oligonucleotides targeted to SEQ ID NO: 1 meet the written description provisions of 35 USC 112, first paragraph. However, the claim are embrace antisense targeted to gene sequences, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or antisense oligonucleotides or constructs targeted thereto, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997);

In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical

characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only antisense constructs and oligonucleotides targeted toSEQ ID NO: 1 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 20-23 embrace methods of antisense based therapy. The instant specification asserts 14 that antisense can be administered to certain cells such as

immune cells or cells of the gastrointestinal tract. At pages 14-15 it id generally described administration of antisense to a whole animal. No specific guidance is provided for delivery of sufficient antisense to a particular cell type for amelioration or treatment of any particular disease. The guidance provided is cursory and provideds no detail for any particular disease treatment, for example.

The art of nucleic acid based therapy is an unpredicatable art. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary

pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*." Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a

useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome. One in the art would be required to perform undue trial and error experimentation to practice the claimed invention. The quantity of experimentation would include the determination of specific antisense sequences that would be effective in vivo and how to delivery sufficient antisense to target cells of a disease contemplated for 14-3-3σ antisense therapy, for example.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prasad et al [US 5,776,676], Weintraub [Scientific American, January 1990, pages 40-46] and James [Antiviral Chemistry & Chemotherapy, Vol. 2(4):191-214, 1991].

The instant invention is drawn to an antisense construct comprising a transcriptional promoter, a transcription terminator, and a DNA segment comprising segments of the 14-3-3σ gene in antisense orientation. The promoter can be inducible.

Prasad et al. Teach a nucleic acid sequence of the HME1 gene which corresponds to the human 14-3-3σ gene of the instant invention. Prasad et al discuss what may be the properties of the HME1 gene (see column 8 lines 30-45, for example).

The work of Prasad et al indicates the use of HME1 as a marker gene for disease states but does not provide for the biological role of HME1, for example.

Weintraub et al have taught that antisense molecules are valuable research tools that can be used to determine the function of genes. It has been taught by Weintraub that antisense methods of determining biological function of genes is superior to those method used in the art prior to antisense technology. Weintraub et al have further taught expression vectors for antisense expression.

James et al have also taught that there are many vectors known in the art at the time of invention that comprised promoters (including inducible) and expression terminators (see Table 1 and page 198, left column, for example).

It would have been obvious to one in the art at the time of invention to use the expression vectors taught by Weintraub and James to express antisense molecules of 14-3-3σ since Weintraub has taught the use of antisense technology as an advantageous method of determining gene function. One in the art would have been motivated to determine the function of HME1 since Prasad et al have taught that HME1 expression is associated with cancer, for example. One would have had a reasonable expectation of success since James et al and Weintraub et al have provided guidance on how to construct vectors for antisense expression in cells in culture for example.

The invention as a whole would therefor have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 16-18 rejected under 35 U.S.C. 103(a) as being unpatentable over Prasad et al (supra), Weintraub (supra), and Baracchini et al [US 5,801,154].

Prasad et al. Teach a nucleic acid sequence of the HME1 gene which corresponds to the human 14-3-3σ gene of the instant invention. Prasad et al discuss what may be the properties of the HME1 gene (see column 8 lines 30-45, for example). The work of Prasad et al indicates the use of HME1 as a marker gene for disease states but does not provide for the biological role of HME1, for example.

Weintraub et al have taught that antisense molecules are valuable research tools that can be used to determine the function of genes. It has been taught by Weintraub that antisense methods of determining biological function of genes is superior to those method used in the art prior to antisense technology. Weintraub et al have further taught expression vectors for antisense expression.

Baracchini et al have taught, at column 6 for example, that antisense oligonucleotides can be used for research purposes and have also taught at column 6 that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use

of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 4 it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

It would have been obvious to one in the art at the time of invention to use the antisense molecules targeted to 14-3-3σ since Weintraub has taught the use of antisense technology as an advantageous method of determining gene function and Baracchini et al have also taught the utility of antisense molecules as research tools. One in the art would have been motivated to determine the function of HME1 since Prasad et al have taught that HME1 expression is associated with cancer, for example. One would have had a reasonable expectation of success since Weintraub et al have provided guidance on how to determine gene function with antisense and Baracchini et al have taught the general guidelines for making antisense to a target gene, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claim 19 rejected under 35 U.S.C. 103(a) as being unpatentable over Prasad et al (supra), Weintraub (supra), and Baracchini et al as applied to claims 16-18 above, and further in view of Prakash et al [J. Am. Chem. Soc Vol 114, 3523-3527, 1992].

Prasad et al (supra), Weintraub (supra), and Baracchini et al are relied upon as above.

None of the above reference teach circular antisense constructs, however, this deficiency is corrected by Prakash et al. Prakash et al have taught the use of circular antisense oligonucleotides and have taught that such triplex forming oligonucleotides have better binding strength than linear analogues. (see page 3527, for example.)

One in the art would be motivated to use circular oligonucleotide for that reason stated above and would have a reasonable expectation of success since Prakash et al have demonstrated that such circular oligonucleotides bind better than linear oligonucleotides, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM
May 28, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635